

***Remarks***

***I. Status of the Claims***

Claims 89-126 are pending in the application.

***II. The Rejection Under 35 USC § 112, First Paragraph***

The Examiner has maintained the rejection of claims 89-126 under 35 USC § 112, first paragraph. Applicants respectfully traverse the rejection.

The Examiner has challenged the enablement of the claimed invention in regard to the development of serum-free cell culture media that support the expansion of embryonic stem cells *in vitro*. According to the Examiner,

[t]he specification fails to provide an enabling disclosure for how to make and use any and all combinations of media supplements, media formulations, and media useful for the claimed methods as the specification does not provide adequate guidance for the selection of appropriate serum-free medium supplements that would support the expansion/differentiation of embryonic stem cells as required by the claims.

Paper No. 7, pages 4-5.

In the present Advisory Action (Paper No. 13), the Examiner has rejected Applicants' contention, as set forth in their previous Reply, that a person of ordinary skill in the art, based on Applicants' disclosure, and with only routine experimentation, would have been able to develop a significant number of operative media formulations within the scope of the present claims. In addition, based on an arithmetic calculation employing various

assumptions, the Examiner asserted that the number of possible combinations of components to be tested for development and optimization of the media formulations would be  $6.8 \times 10^{10}$ . See Paper No. 13, page 3. Even if the Examiner's calculation were considered completely accurate, Applicants maintain that the Examiner has nonetheless failed to establish a *prima facie* case of non-enablement.

In order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. See *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." See *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original).

In the previous Office Actions (see Papers No. 5 and 7), as well as in the present Advisory Action, the Examiner has evidently placed the initial burden on Applicants to prove that the specification enables the full scope of the claimed invention. Under *Marzocchi*, this is improper. In addition, the Examiner has not provided any evidence or sound scientific reasoning demonstrating that the skilled artisan would require more than routine experimentation to develop specific additional serum-free culture medium formulations, based upon the guidance and teachings of the present application, and use one or more of these formulations to expand embryonic stem cells *in vitro*. Rather, the Examiner has merely set forth a mathematical calculation purporting to illustrate that a large number of medium formulations could possibly be made. Applicants submit that the existence of

a large number of possible combinations in and of itself is insufficient to satisfy the Examiner's burden in establishing a *prima facie* case of non-enablement. Guided by Applicants' disclosure, one of ordinary skill in the art could easily prepare a serum-free medium and test it for use in the claimed method with no more than routine experimentation.

The Examiner has also challenged the enablement of the claimed invention based on the embryonic stem cells *per se* that are contemplated for use within the scope of the present claims. According to the Examiner, while the specification is enabling for methods of culturing the embryonic stem cell lines exemplified in the disclosure, "the specification is not enabling for culturing any embryonic stem cell in the absence of a feeder layer utilizing the broadly claimed medium supplements. . ." See Paper No. 7, page 3. In the present Advisory Action, the Examiner further stated:

Even if the claims were enabled with respect to putative embryonic stem cells from species taught in the prior art references [as cited by Applicants in their previous Reply], there is no objective evidence of record that the medium formulation, which is effective in supporting murine embryonic stem cell expansion *in vitro*, would be effective in supporting expansion of embryonic stem cells obtained from other species.

Paper No. 13, page 3.

The above quotation clearly indicates that the Examiner, rather than setting forth evidence that demonstrates the non-enablement of Applicant's claims, has instead imposed the initial burden on Applicants to prove the enablement of the claimed invention. Such burden shifting is improper since it is the Examiner, not the Applicant, who has the initial burden regarding enablement. See *Marzocchi*, 439 F.2d at 224, 169 USPQ at 370; see also *Wright*, 999 F.2d at 1562, 27 USPQ2d at 1513. Since the Examiner has failed to set forth

specific evidence or sound scientific reasoning indicating that the present invention is non-enabled with respect to the *in vitro* expansion of a broad range of embryonic stem cells as encompassed by the present claims, the Examiner has not satisfied her initial burden under 35 USC § 112, first paragraph.

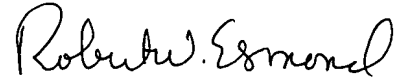
### ***III. Conclusion***

Applicants maintain that the Examiner has not set forth acceptable objective evidence or sound scientific reasoning showing that undue experimentation would have been required for one of ordinary skill in the art to make and use the invention commensurate in scope with the present claims. Thus, the Examiner has not satisfied her burden in establishing a *prima facie* case of non-enablement. Accordingly, Applicants respectfully request that the rejection of claims 89-126 under 35 USC § 112, first paragraph, be reconsidered and withdrawn.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

A handwritten signature in black ink, reading "Robert W. Esmond". The signature is written in a cursive style with a large, stylized "R" and "E".

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